In silico study of Ferula latisecta-derived compounds molecular interactions with α-glucosidase

Eurasian Clinical and Analytical Medicine Original Research

Molecular interactions of Ferula latisecta

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Abstract

Aim: Our study aimed to investigate the sulfur compounds' antidiabetic effect in Ferula latisecta.

Material and Methods: The molecular docking method investigated the α-glucosidase inhibitory effect of the components. In our study, the pharmacokinetic properties of Ferula latisecta compounds were also investigated with the SwissADME method, and the toxicity risk analyzes were investigated with Protox II tools. Ferula latisecta compounds were drawn from the literature in Chemdraw and and α-glucosidase enzyme structure was obtained from Protein Data Bank. Finally, the molecular interaction analysis between α-glucosidase and compounds from Ferula latisecta was performed by AutoDock 1.5.7. Molecular interactions were investigated using Discovery Studio Visualizer and Ligplot 2.1 program.

Results: All the selected sulfur compounds from Ferula latisecta followed Lipinski's rules, had sufficient binding energy, and lacked toxicity; therefore, they were appropriate candidates for α-glucosidase inhibition. Among these compounds, 2-(4-hydroxyphenyl) ethyl lignocerate and isosco-poletin showed the lowest binding energy and the highest inhibitory effect on α-glucosidase enzyme with −9.1 and −7.7 kcal/mol, respectively.

Discussion: These compounds also indicated a lower binding energy than the standard inhibitor (miglitol). Among the sulfur compounds in Ferula latisecta 2-(4-hydroxyphenyl) ethyl lignocerate and isoscopoletin were predicted to be the potent inhibitors due to having more hydrogen bonds and hydrophobic interactions with the active site of α-glucosidase.

Keywords

In Silico, α-Glucosidase Inhibition, Molecular, **Ferula latisecta**, Diabetes

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Introduction

Diabetes mellitus (DM) continues to be a significant threat to human health today, and it is estimated that by 2045, the number of patients worldwide will exceed 642 million [1]. DM is a chronic metabolic disease characterized by high blood sugar levels due to insulin resistance [1,2]. High blood glucose levels also damage blood vessels and nerves, causing various health problems such as hypertension, cardiovascular disease, blindness, stroke, amputations, kidney, and dental conditions [3,4,5]. Although different drug treatments are available today, the side effects of drugs continue to be a problem.

Antidiabetic drugs fall into several categories, including sulfonylureas, bioguanidines, insulin mimetics (glucagon-like peptide analogs), and α-glucosidase inhibitors.

The discovery of new drugs is essential because of the side effects of existing antidiabetic drugs. Academic studies have recently confirmed medicinal plants' beneficial effects in treating diabetes [6,7]. Researched impacts of plants include improving glycemic control, lowering serum lipid levels, inhibiting oxidative stress, and improving inflammatory response [8,9].

The genus Ferula is mainly distributed throughout central and Southwest Asia (especially Iran and Afghanistan), the Far East, North India, and the Mediterranean. The main phytochemicals present in the genus are as follows: coumarin, coumarin esters, sesquiterpenes, sesquiterpene lactones, monoterpene, monoterpene coumarins, prenylated coumarins, sulfur-containing compounds, phytoestrogen, flavonoids, and carbohydrates [10].

People used these plants' roots, leaves and fruits as vegetables, spices, or medicine. In addition, other species of this genus have been reported to be popularly used for sedatives, digestive disorders, rheumatism and arthritis, neurological disorders, inflammations, dysentery, headaches, and toothaches [11,12].

Ferula latisecta (F. latisecta) has been used in Iranian folk medicine to treat parasitic diseases, relieve stomachaches in infants, and to control diabetes. In other studies, it has been shown that essential oil obtained from the above-ground parts of **F. latisecta** has an antimicrobial effect [13,14].

In a previous study, streptozotocin-induced diabetic male Wistar rats were treated with **F. latisecta** root (400 mg/kg/day) for four weeks, resulting in significantly reduced LDL levels in the kidney and liver ($p < 0.05$) and thiol ($p < 0.05$) and superoxide dismutase ($p < 0.01$). In addition, the root of **F. latisecta** was found to reduce serum total cholesterol levels ($p < 0.05$) and prevent the progression of hyperglycemia [15].

The mechanism of action of many drugs used to treat diabetes occurs through the inhibitory effect of α-glucosidase (AG). AG is a carbohydrate hydrolyzing enzyme. Overactivity of α-glucosidase causes glucose to be absorbed by the small intestinal lumen and enter the bloodstream. Glucose release results in increased blood glucose levels and uncontrolled hyperglycemia in type-2 DM patients. α-Glucosidase is one of the glucosidase enzymes responsible for the mechanism of DM. α-glucosidase catalyzes the hydrolysis reaction by breaking the α-(1,4)-glycosidic bond of carbohydrates to become a free monosaccharide (α-D-glucose) before entering the bloodstream. The AG enzyme plays a vital role in carbohydrate metabolism by converting starch and disaccharides into glucose [16]. As a result of inhibiting the enzyme α-glucosidase, carbohydrate digestion slows down and causes glucose to enter the bloodstream later. As a result, it constitutes a proper prophylactic treatment for hyperglycemia [17]. Therefore, inhibition of AG is a practical therapeutic approach for treating DM.

Our study aims to determine the toxicity of eight compounds [12] of **F. latisecta** by in silico methods and investigate the anti-diabetes effect by examining the inhibitory effect of the compounds on the α-glucosidase enzyme by molecular docking method.

Material and Methods

First, important sulfur-containing phenolic compounds were obtained from the literature on **F. latisecta** [12]. Next, compounds were drawn using ChemDraw software. Finally, a suitable crystallographic structure with a resolution of 1.60A with the code PDB ID 3A4A from the α-glucosidase enzyme protein data bank was obtained from the protein database (https://pubchem.ncbi.nlm.nih.gov/).

Determination of pharmacological properties of compounds by Lipinski parameter

The potentially effective sulfur compounds of **F. latisecta** were evaluated using the Lipinski parameter to inhibit the activity of the α-glucosidase enzyme. All the compounds showed the properties required by Lipinski's parameter; therefore, they were predicted to have optimal adsorption. The SwissADME database (http://www.swiss adme.ch/ index .php) was used to obtain the Lipinski properties of the compounds.

Evaluating the toxicity of the selected compounds

F. latisecta contains many sulfur compounds. Among the most highlighted sulfur compounds, latisulfide A, latisulfide B, latisulfide C, latisufide D, and latisulfide E, τ-cadinol, 2-(4-hydroxyphenyl) ethyl lignocerate and isoscopoletin are also found in this plant. Phenolic compounds: Lack of toxicity is one of the critical factors for choosing a compound as a therapeutic candidate. Therefore, in this study, the toxicity of each of the sulfur compounds, such as liver toxicity, carcinogenicity, immunotoxicity, mutagenicity and the toxicity class of the compounds were examined using the Protox tool (https://bio. tools/protox) [18]. In addition, the accuracy of the toxicity analysis performed with the PKCSM software (https://biosig.lab.uq.edu.au/ pkcsm/prediction) was checked.

Molecular interaction analysis

This study used the Autodock vina tool (version 1.5.7) [19] to investigate the molecular interaction between α-glucosidase enzyme and selected ligands. Before the docking analysis, the enzyme structure was optimized by removing excess ligands and water molecules using the BIOVIA Discovery Studio 2021 program. The Spartan 14 (Version 1.1.4) program optimizes all compounds for energy. Kollman charges were determined by adding polar hydrogens to the protein using the AutoDock vina 1.5.7 tool. The partial load of the compounds was calculated using Compute Gasteiger in AutoDock 1.5.7 tool.

The x, y, and z coordinates were determined to bind the α-glucosidase enzyme to its catalytic site (x:20.53, y: -10.11 z:22.38 x:40, y:40 z:40). Finally, molecular interactions and binding types between the selected compounds and the α-glucosidase enzyme were investigated using the Discovery Studio visualizer and Ligplot (version 2.2.8) programs [20].

Results

Pharmacological properties of the selected compounds

The selected ligands: latisulfide A, latisulfide B, latisulfide C, latisufide D, latisulfide E, τ-cardinal, 2-(4-hydroxyphenyl) ethyl lignoceric and isoscopoletin were obtained from the literature and drawn in ChemDraw software [12].

Toxicity analysis of the selected compounds

The compounds were also evaluated for their toxicity and toxicity class. The criterion for selecting a compound as a drug candidate is the safety of the compound, and the compound should not show any toxicity.

Compounds contained in **F. latisecta** were evaluated in terms of toxicity and toxicity class. In the ADME study conducted on SwissADME software (http://www.SwissADME.ch/), it was found to be appropriate among the compounds in terms of pharmacokinetic properties, except for 2-(4-hydroxyphenyl) ethyl lignocerate. Toxicity estimation was

evaluated with the protox II tool program. According to the protox II tool prediction program, it was observed that hepatotoxic and immunotoxic effects may occur in all compounds. However, when we look at the probability values, it has been determined that the risk of toxicity is low. Toxicity class 4 indicates low toxicity of the ingredients. When the PKCSM program, which is a different software, was examined separately, no toxicity was detected.

Molecular interaction analysis

The results of the molecular interaction between the selected compound

Table 1. Investigation of pharmacologic parameters (Drug-like) for sulfur compounds in **F. latisecta** according to Lipinski rule.

Compound	Hydrogen bond donors (≤5)	Hydrogen bond acceptors (≤10)	Molecular mass (<500)	Log (<5)
Latisulfide A	0	4	220.36	3.24
Latisulfide B	0	4	246.40	3.80
Latisulfide C	0	4	260.42	4.19
Latisulfide D	1	3	178.32	2.67
Latisulfide E	1	4	354.49	4.65
τ-cadinol	1	1	222.37	3.78
2-(4-hydroxyphenyl) ethyl lignocerate	1	3	460.74	9.30
isoscopoletin	1	4	192.17	1.51

Table 2. Evaluation of toxicity and toxicity class of the selected Ferula latisecta compounds.

Compound	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity
Latisulfide A	H	NC	I	NM
Latisulfide B	H	NC	I	NM
Latisulfide C	H	NC	I	NM
Latisulfide D	H	NC	I	NM
Latisulfide E	H	NC	I	NM
τ-cadinol	H	NC	I	NM
2-(4-hydroxyphenyl) ethyl lignocerate	H	NC	I	NM

H: hepatotoxicity, NC: no carcinogenicity, NM: no mutagen, I: immunotoxicity

Table 3. Interaction and binding energy of sulfur compounds with amino acids of α-glucosidase.

Compounds	Binding energy (Kcal/mole)	Hydrogen interaction	Hydrophobic interaction
Latisulfide A	-6.2	Arg442	Phe303, His280
Latisulfide B	-6.5	-	Phe178, Arg315, His280
Latisulfide C	-6.6	Arg315	Lys156, Arg315, Tyr158, Phe159, Phe178
Latisulfide D	-5.5	Asp215, Asp352	Tyr158, Phe178, Val216, Phe159
Latisulfide E	-7.1	Tyr407, Glu405	Trp36
τ-cadinol	-7.7	-	Tyr158, Tyr316, Phe314, Arg315
2-(4-hydroxyphenyl) ethyl lignocerate	-9.1	Pro66	Pro151, Trp238, Val410
isoscopoletin	-7.7	Ser236, Asn235, Glu429, Asn317	Ile419, His423
Miglitol (Standard compound)	-7.1	Gln353, Arg442	

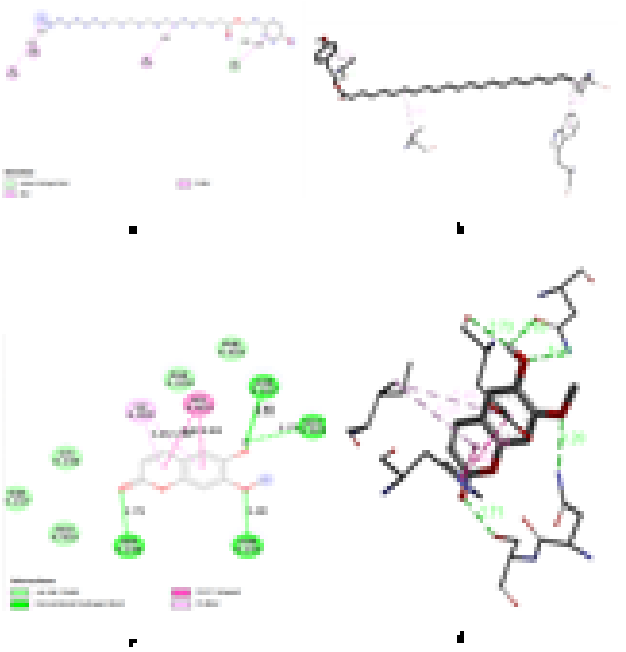

Figure 1. Two-dimensional (2D) and three-dimensional (3D) plots of α-glucosidase interactions with selected potential inhibitors.
a) 2D representation of the molecular interactions between enzyme 2-(4-hydroxyphenyl) ethyl lignocerate b) 3D representation of molecular interactions between enzyme and 2-(4-hydroxyphenyl) ethyl lignocerate. c) 2D representation of molecular interactions between enzyme and isoscopoletin. d) 3D representation of molecular interactions between enzyme and isoscopoletin.

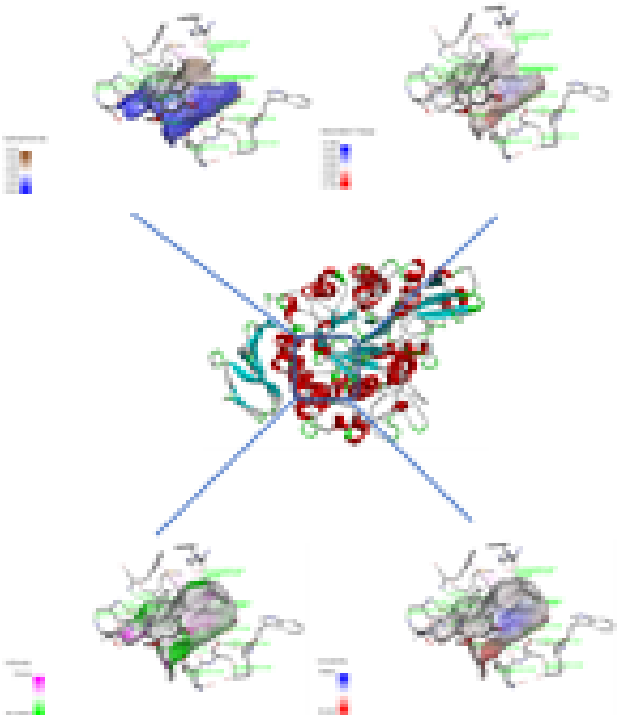

Figure 2. Three-dimensional representation of the receptor and isoscopoletin ligand surface interactions in the active site of α-glucosidase regarding polarity, hydrogen bonding, hydrophobic and ionized surface of the exchanges.

and the α-glucosidase enzyme obtained by molecular coupling assay are given in Table 1. All compounds showed good binding with the enzyme. The binding energy, hydrogen and hydrophobic interactions between the compounds and the enzyme are also presented in Table 3. The results of the molecular docking study showed that all sulfur compounds in **F. latisecta** can bind to the active site of α-glucosidase and inhibit the activity of this enzyme. According to the docking analysis, the binding energies of the studied compounds are different; therefore, the critical energy ranges from –5.5 to –9.1 kcal/mol. The lower the binding energy level (negative), the stronger the binding between the receptor (enzyme) and ligands (compound or inhibitor). Among the selected sulfur compounds, 2-(4-hydroxyphenyl) ethyl lignoceric with a value of -9.1 kcal/mol and isoscopoletin with a weight of -7.7 kcal/mol showed the lowest binding energy. Therefore, they are estimated to provide the highest inhibitory effect among the compounds.

Previous studies have shown that amino acids such as LYS-156, GLN-279, HIS-280, PRO-312 GLU-277, ASP-352, ASN-415, and ARG-442 play a key role in the interaction of enzyme and inhibitor in the active site of α-glucosidase [21]. Miglitol was used as a standard α-glucosidase inhibitor. The insertion results showed that miglitol, with a binding energy of -7.1 kcal/mol, has a significant binding energy and hydrogen bonding with amino acids Gln353 and Arg442.

Pro66 (3.60 and 5.50 Å) 2-(4-hydroxyphenyl) ethyl lignoceric complex and isoscopoletin complex with amino acids Ser236, Asn235, Glu429, Asn317 also have hydrogen bonds (Figure 1 a,b). Isoscopoletin showed more hydrogen bond interactions than other compounds. These two compounds have lower binding energies than other compounds. This also shows that it can bind more strongly to the enzyme. Figure 1 shows the three-dimensional view of the ionization, hydrophobic, polar, and hydrogen bonding reactions between α-glucosidase and isoscopoletin.

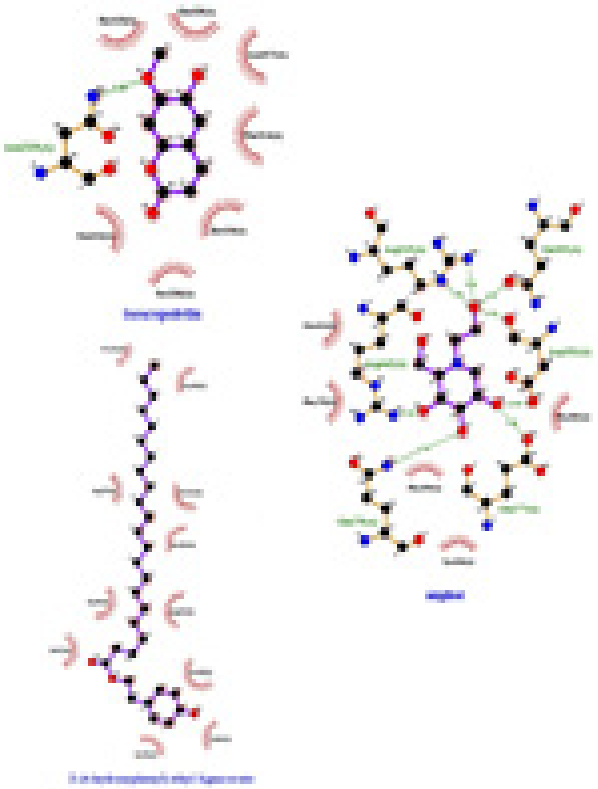

Figure 3. Comparison of isoscopoletin and 2-(4-hydroxyphenyl) ethyl lignocerate miglitol (standard inhibitor) in the active site of α-glucosidase enzyme.

Discussion

In the present study, 2-(4-hydroxyphenyl) ethyl lignoceric has shown that **F. latisecta** has the lowest binding energy among the phenolic compounds. In another study, while the synthesis and inhibitory potentials of sulfur compounds were investigated, it was found that compounds such as methazolamide, acetazolamide, and timolol (having sulfur atoms with binding energies of -4.3, -4.8 and 4.5, kcal/mol in their structure, respectively) inhibited the α-glucosidase enzyme significantly [22]. In this study, with a -9.1 kcal/mol value, 2-(4-hydroxyphenyl) ethyl lignocerate showed the best inhibition value among sulfur compounds.

In addition, miglitol did not show any hydrophobic interaction with α-glucosidase. However, it showed hydrophobic interactions with 2-(4-hydroxyphenyl) ethyl lignoceric and α-glucosidase Pro151, Trp238, and Val410. Exchange of isoscopoletin with α-glucosidase showed hydrophobic interaction with amino acids Ile419 and His423.

Conclusion

When we looked at the results of our study, it was clear that the pharmacokinetic properties of important sulfur compounds were good. Still, hepatotoxicity and immunotoxicity risk were observed in all components; however, the low toxicity probability levels and the toxicity class 4 show that it does not carry a significant stake in toxicity. Also, the hepatotoxic effects of hepatotoxic compounds were examined in a different software PKCSM program. When the data obtained from this program were analyzed, it was seen that they were not toxic. Based on the results of the docking study, it can be concluded that of the eight compounds in **F. latisecta**, 2-(4-hydroxyphenyl) ethyl lignocerate and isoscopoletin are more effective in inhibiting the α-glucosidase enzyme. These compounds also exhibited lower binding energies compared to miglitol. Therefore, they are likely to be more potent inhibitors than miglitol. Considering that in silico studies are used for preliminary studies and predictions, it is thought that the results of our study should be validated with in vivo and in vitro studies.

A comparison of 2-(4-hydroxyphenyl) ethyl lignocerate and isoscopoletin with miglitol is shown. Both selected compounds appear to interact with different amino acids in the catalytic pocket of the α-glucosidase enzyme.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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